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A Randomized, Double-blind,
Placebo-controlled Trial***

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Lack of effectiveness of the 23-valent polysaccharide pneumococcal vaccine in reducing all-cause pneumonias among healthy young military recruits: A randomized, double-blind, placebo-controlled trial



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ABSTRACT

Background: *Streptococcus pneumoniae* infections have periodically caused significant morbidity and outbreaks among military personnel, especially trainees. This study evaluated the effectiveness of the 23-valent polysaccharide pneumococcal vaccine (PPV23) in reducing pneumonia in healthy military trainees.

Methods: From 2000–2003, 152 723 military trainees from 5 US training camps were enrolled in a double-blind, placebo-controlled trial of PPV23. Participants were closely monitored during basic training for radiographically confirmed pneumonia etiology and loss-of-training days. Participants were also followed using electronic medical encounter data until 1 June 2007 for three additional outcomes: any-cause pneumonia, any acute respiratory disease, and meningitis.

Results: Comparison of demographic data by study arm suggested the randomization procedures were sound. During basic training, 371 study participants developed radiographically confirmed pneumonia. None had evidence of *S. pneumoniae* infection, but other etiologies included adenovirus (38%), *Chlamydia pneumoniae* (9%), and *Mycoplasma pneumoniae* (8%). During the follow-up period, many study participants, in both the vaccine and placebo groups, had clinical encounters for the medical outcomes of interest. However, Cox's proportional hazard modeling revealed no evidence of a protective vaccine effect during recruit training (radiographically confirmed pneumonia) or up to 6.7 years after enrollment (any-cause pneumonia, any acute respiratory disease, or meningitis).

Conclusions: Data from this large, double-blind, placebo controlled trial do not support routine use of PPV23 among healthy new military trainees. This clinical trial was registered at clinicaltrials.gov (registration number NCT02079701, <http://www.clinicaltrials.gov/ct2/show/NCT02079701?term=NCT02079701&rank=1>).

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1. Background

Streptococcus pneumoniae infections are recognized to cause significant morbidity and mortality especially among persons younger than 2 and older than 65 years of age. The 23-valent polysaccharide pneumococcal vaccine (PPV23) was first approved for use in the United States in 1983 [1,2]. Initially it was recommended for children older than 2 years of age and adults with chronic illnesses, as well as for adults aged 65 years or older [2]. Numerous studies were conducted evaluating the effectiveness of this vaccine in various populations. Inconsistent protection against

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community-acquired pneumonias was noted, but later studies more consistently demonstrated the vaccine's best protection was against invasive pneumococcal disease [3–9].

S. pneumoniae is recognized as a major cause of morbidity among US military populations. During the influenza pandemic from 1918 to 1919, death was far more common among patients with influenza who developed secondary *S. pneumoniae* infection [10]. This predisposition to *S. pneumoniae* or bacterial infection after influenza infection has subsequently been well described [11]. Additionally, a study by Hakansson and colleagues in the early 1990s documented increased adherence of *S. pneumoniae* to human respiratory tract epithelial cells previously infected with adenovirus, suggesting an increased expression of receptors for *S. pneumoniae* after adenovirus infection [12]. This is particularly important to consider in the military training setting where adenovirus infections are prevalent [13].

US Navy data from 1981 to 1991 suggest that *S. pneumoniae* caused approximately 12% of military pneumonia hospitalizations or 9.5 admissions per 100 000 person-years [14,15]. An epidemic of 124 cases of pneumococcal pneumonia occurred during winter 1989 at a military training facility. Reichler et al. suggested that PPV23 be used as a preventive strategy where potential exposure to respiratory pathogens occurs in crowded settings such as these military training camps [16]. Other outbreaks have been documented, particularly in US military training scenarios [14,17,18]. Pneumococcal pneumonia outbreaks have also occurred in Israel, Russia, and Finland [19–21]. Because the incidence of outpatient disease is unknown and there are diagnostic difficulties in identifying *S. pneumoniae*, these reports likely underestimate the true impact of this pathogen [14].

Civilian cost-benefit and cost-effectiveness studies performed prior to this study suggested that vaccination against pneumococcal pneumonia would create net health improvements in every age group and that vaccination programs for those considered at high risk were economically justified [22,23]. Beutels and Postma demonstrated that vaccination of those between 65 and 75 years of age, immunocompromised individuals, and military populations was cost-effective [24]. In 2000, Vold Pepper and Owens suggested that if all Navy and Marine Corps members were vaccinated, savings of \$5.7 million could be achieved during members' active-duty service [25].

An increasingly important problem regarding *S. pneumoniae* infections is antimicrobial resistance. Data collected from the United States for the SENTRY Antimicrobial Surveillance Program beginning in 1998 showed an overall increasing trend of *S. pneumoniae* non-susceptibility to penicillin, amoxicillin, ceftriaxone, erythromycin, and clindamycin [26]. From 1998 to 2011, percent susceptible *S. pneumoniae* isolates dropped from 97.1 to 81.1 for amoxicillin ($\leq 2 \mu\text{g/mL}$); from 96.8 to 85.2 for penicillin ($\leq 2 \mu\text{g/mL}$); and from 82.2 to 55.2 for erythromycin ($\leq 0.25 \mu\text{g/mL}$) [26]. Prior to this study, data from Naval Medical Center San Diego from May 1995 to May 1997 showed that the prevalence of penicillin resistance among non-sputum clinical isolates of *S. pneumoniae* was as high as 43% (18% intermediately resistant, 25% highly resistant) [27]. As the prevalence of antibiotic resistance increases in military populations, alternate public health interventions, such as routine pneumococcal vaccination of all military trainees, have been considered [14].

With frequent outbreaks, potential cost savings, increasing resistance to antibiotics, and the availability of the safe PPV23, public health officials at several US military training centers have opted to routinely employ the vaccine, despite the lack of effectiveness data and a specific policy requirement. A number of scientific reports posit success with the vaccine among military trainees in the United States, Russia, and Finland [17,19,21,28]. In 1998, to address the need for compelling data, the US Armed Forces

Epidemiological Board (USAFEB), a volunteer board composed of civilian experts in various fields of infectious disease and public health, recommended the US Department of Defense (DoD) conduct a research study on the effectiveness of the pneumococcal vaccination in military populations [29]. The hope was that the PPV23 might be clearly established to reduce morbidity and mortality within military groups already known to bear a high burden of respiratory illness, and address the need for more evidence to guide policy decisions for pneumococcal vaccination in military populations. Spurred by the USAFEB's recommendation, the goal of this study was to determine the effects, if any, of PPV23 on the outcome measures of *S. pneumoniae* infections, any-cause pneumonia, any-cause respiratory disease, recruit training clinical pneumonia (radiographically confirmed during the recruit training period), and days lost from training among military recruits.

2. Methods

2.1. Study participants, enrollment, and follow-up

Given their documented high rates of respiratory illness, US military trainees were selected for participation. The procedures followed were in accordance with DoD ethical standards and the Helsinki Declaration of the World Medical Association. The study was approved by multiple DoD institutional review boards. Using a written informed consent process, basic training recruits at five recruit training centers (in South Carolina—two sites, Missouri, Illinois, and California), where rates of respiratory illness are consistently high, were invited to participate during their first week of training. Pregnancy screening was performed on all women, and those with positive results were not enrolled. Exclusion criteria included known history of PPV23 vaccination within the past 5 years or having a medical condition that either required or precluded pneumococcal vaccination. Study participants completed a study questionnaire and were administered a prepackaged, blinded, and randomized intramuscular deltoid injection containing either the PPV23 (Wyeth Pharmaceuticals or Merck & Co., Inc.) or saline. Randomization was conducted by a third party in a simple 1:1 ratio, and tubes were labeled with a unique identifier. The identifier was then followed on each subject's enrollment paperwork for later unblinding. Study injections were administered at the same time as other recruit in-processing vaccinations, which may have included vaccines against polio, measles–mumps–rubella, varicella, tetanus–diphtheria, hepatitis A virus, hepatitis B virus, meningococcal disease (A/C/Y/W135), and influenza. At the end of recruit training, a questionnaire was administered to capture symptoms and signs of illnesses that might have been missed by the active and passive surveillance.

Since enrollment continued for more than 2 years, the person-year contributions of those first enrolled were greater than those enrolled near the trial's end. The original planned surveillance period was 1.7 years. This was later extended to 6.7 years from enrollment of the first participant, for continued monitoring of impact in this large double-blinded trial.

2.2. Specimen collection

During the active surveillance period, study participants with suspected pneumonia were identified by the attending physician. Study personnel obtained three throat swabs, blood cultures (aerobic and anaerobic), sputum sample (if producible), and acute serum samples from participants. Samples were processed on all participants that received radiological confirmation. From these, attempts were made to also capture a convalescent serum sample 2 weeks after the acute presentation. These attempts were not always

successful. Barriers included trainee discharge from military service, difficulty in obtaining access to the recruits when they were in field exercises, and recruits graduating and moving to new duty stations.

2.3. Laboratory methods

Specimens collected from study participants were examined using classic, molecular, and serologic laboratory methods at the Naval Health Research Center (NHRC) Respiratory Disease Laboratory, a College of American Pathologists-accredited laboratory.

At NHRC, researchers isolated adenovirus, influenza, parainfluenza, and respiratory syncytial virus from pharyngeal swabs using fluorescent antibody antigen tests. Adenovirus and influenza isolates were typed using standard viral identification techniques [29].

Sputum specimens were inoculated for *S. pneumoniae* culture using standard techniques [30].

Paired acute and convalescent sera were assessed for IgM and IgG titers to pneumolysin. Sera were tested with an enzyme immunoassay using a procedure described by Kalin et al. [32].

For *Chlamydia pneumoniae* polymerase chain reaction study, throat swabs were collected from patients diagnosed with pneumonia, immediately placed in Chlamydia transport media, and transported on ice. The throat swabs were used in a direct PCR method, such as the procedure described by Campbell et al. [33]. Amplification products were analyzed by electrophoresis through a 1.5% agarose gel by standard methods [34]. Sample preparation, PCR amplification, and analysis of amplification products were performed in separate rooms.

To assess *Mycoplasma pneumoniae*, a throat swab was collected and immediately placed into 2.0 mL of *M. pneumoniae* transport media (SP4 broth). Culturing, subculturing, and molecular testing were performed as per previously published protocols [35–37].

2.4. Capturing disease outcomes

Outcome measures included *S. pneumonia* infections, any-cause pneumonia, any-cause respiratory disease, recruit training clinical pneumonia (radiographically confirmed during the recruit training period), and days lost from training. Active surveillance was conducted for radiographically confirmed pneumonias only during the recruit training period (12 weeks for Marines and 9 weeks for Army and Navy). Passive electronic monitoring of health care encounters for outcomes other than clinical pneumonia took place during recruit training and at the subsequent duty stations using the DoD comprehensive electronic databases of outpatient health care encounters, inpatient encounters, and encounters at civilian facilities billed to the DoD. *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes 480–486 and 487 were monitored for these outcomes throughout the entire study period. Meningitis cases (ICD-9-CM codes 320–320.2, 320.9, and 322.9) were also captured through these electronic databases.

2.5. Statistical analysis

A target sample size of 166 744 person-years was calculated based on the following assumptions: 12% attrition from military training, clinical pneumonia attack rate of 11 cases per 1000 person-years, 20% of captured pneumonias caused by *S. pneumoniae*, 90% of captured *S. pneumoniae* pneumonias caused by a vaccine-covered *S. pneumoniae* strain, and 70% vaccine efficacy.

After descriptive investigation of population characteristics, univariate analyses were performed to assess the significance of associations between demographic variables with acute

respiratory infection, pneumonia, and radiographically confirmed pneumonia.

Active surveillance time was calculated from the participant's enrollment date to the projected completion of training, or diagnosis with radiographically confirmed pneumonia. Passive surveillance time was calculated from the date of enrollment to 1 June 2007, diagnosis with pneumonia or acute respiratory infection, or separation from active-duty service, whichever occurred first.

Using regression diagnostics, collinearity among variables was investigated. Cox's proportional hazard time-to-event modeling was used to evaluate outcomes among study participants, while adjusting for differences in population characteristics between treatment arms and accounting for different enrollment dates and active and passive surveillance periods. A manual backward stepwise elimination approach was used to reduce the saturated Cox regression model by removing those variables that were insignificant ($\alpha = 0.05$) and not confounding other measures of association. Additionally, cumulative probabilities of outcomes from enrollments through end of follow-up periods were graphed. Statistical modeling to produce adjusted hazard ratios and associated 95% confidence intervals was performed using SAS software, version 9.0 (SAS Institute, Inc., Cary, NC).

Days lost from training were estimated using a survey administered at the end of training to a convenience sample of 71 692 study participants. Differences between treatment arms were evaluated using analysis of variance.

3. Results

3.1. Study cohort and demographic characteristics

Enrollment began in October 2000 and was completed in June 2003. A total of 152 723 participants were enrolled and followed, exceeding the required sample size of at least 166 744 person-years for the initially planned observation period. Because of the expanded study observation period, participants were followed for study outcomes until they left military service or 1 June 2007, whichever came first, yielding a total of 617 817.8 person-years of observation. Volunteer rates averaged 46%. The randomization process generated vaccine and placebo treatment groups that were relatively balanced by demographic characteristics (Table 1).

3.2. Outcome measures

No *S. pneumonia* infections were identified by culture, PCR or paired serology ($n = 117/371$ with convalescent draw); therefore, this outcome measure was not included in further analyses.

Using the radiographically confirmed pneumonias captured during recruit training as an outcome, cumulative Cox time-to-event data (days to radiologic diagnosis) documented little difference in study arms (Fig. 1). Similarly, Cox proportional hazard modeling revealed no statistically significant difference in study arms for any-cause pneumonia, any-cause respiratory disease, or meningitis (Fig. 1). Among the 71 692 participants who completed the end of training questionnaire, no significant difference in lost days of training was noted in aggregate (41 129 vs 41 452, for vaccine vs placebo) or when stratified by training site (data not shown). The highest number of radiographically confirmed pneumonias (218 of 371 cases) was reported by Recruit Training Command Great Lakes, which enrolled 26% of participants. A probable etiology was found for 53% of 371 cases of radiographically confirmed pneumonia. Adenovirus infection was identified in 36%, *C. pneumoniae* was identified in 9%, and *M. pneumoniae* was identified in 8% of cases (Table 2). It should be noted that *C. pneumoniae* may be found in

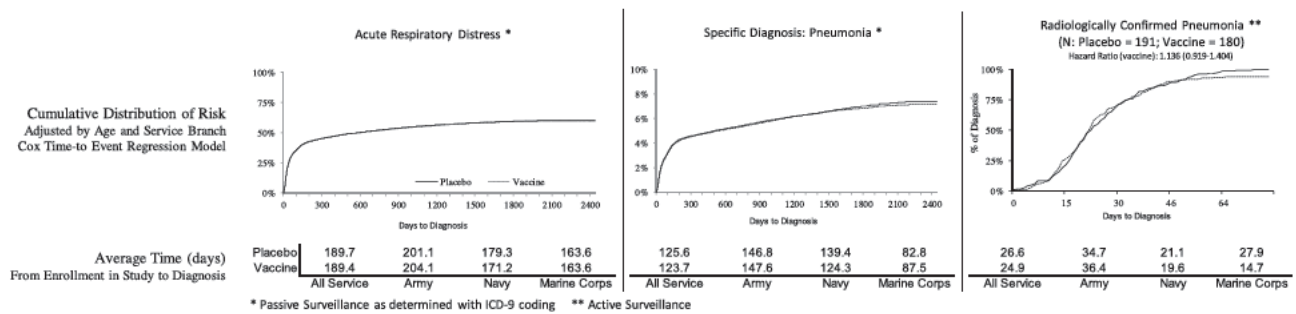


Fig. 1. Cumulative risk of any-cause respiratory disease, any-cause pneumonia, and radiographically confirmed pneumonia by study arm, adjusted for age, race/ethnicity, and sex by Cox proportional hazard modeling.

healthy individuals, so its isolation is not definitive proof of etiology. Although clinical diagnosis is recognized as difficult, no study participant had laboratory evidence of *S. pneumoniae*.

During the follow-up period, many of the study participants had clinical encounters for the medical outcomes of interest: acute respiratory disease (83 209 encounters), pneumonia (6775 encounters), and meningitis (33 encounters). Calculated Cox proportional hazard ratios for acute respiratory disease showed no statistically significant difference between study arms (Table S1).

Table 1
Characteristics of study participants after randomization into the placebo-controlled, 23-valent polysaccharide pneumococcal vaccine trial.

Characteristics	Vaccine group		Placebo group	
	N	%	N	%
Age, y				
17–18	28 489	37.4	28 624	37.4
19–20	24 988	32.8	24 752	32.4
<20	22 768	29.9	23 102	30.2
Sex				
Male	57 678	75.8	57 800	75.7
Female	18 422	24.2	18 555	24.3
Race/ethnicity				
White	43 799	57.4	43 545	56.9
Black	12 453	16.3	12 541	16.4
Hispanic	7506	9.8	7335	9.6
Other	12 487	16.4	13 057	17.1
Enrollment site				
USATC Fort Jackson, SC	21 025	27.6	21 268	27.8
USATC Fort Leonard Wood, MO	23 208	30.4	23 056	30.1%
RTC Great Lakes, IL	19 914	26.1	19 908	26.0%
MCRD San Diego, CA	823	1.1	823	1.1
MCRD Parris Island, SC	11 275	14.8	11 423	14.9

Abbreviations: MCRD, Marine Corps Recruit Depot; RTC, Recruit Training Command; USATC, US Army Training Center.

Table 2
Comprehensive laboratory assay results from 371 patients with radiographically confirmed pneumonias identified during the active surveillance period.

Recruit training site	Radiographically confirmed pneumonia		Adenovirus		Influenza A virus		Parainfluenza virus type 3		Mycoplasma pneumoniae		Chlamydia pneumoniae		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
USATC Fort Jackson, SC	27	7	3	11	0	0	0	0	2	7	0	0	5	19
USATC Fort Leonard Wood, MO	100	27	19	19	1	1	0	0	7	7	8	8	35	35
RTC Great Lakes, IL	218	59	106	49	0	0	0	0	15	7	22	10	143	66
MCRD San Diego, CA	6	2	0	0	0	0	0	0	2	33	0	0	2	33
MCRD Parris Island, SC	20	5	4	20	0	0	1	5	3	15	2	10	10	50
Total	371		132	36	1	0	1	0	29	8	32	9	195	53

Abbreviations: MCRD, Marine Corps Recruit Depot; RTC, Recruit Training Command; USATC, US Army Training Center.

No study participants with pneumonia had laboratory evidence of *Streptococcus pneumoniae*, respiratory syncytial virus, or parainfluenza virus type 1 or 2 infections. Assay results from 371 patients with radiographically confirmed pneumonias identified during the active surveillance period.

4. Discussion

This study represents one of the largest blinded, placebo-controlled trials ever conducted with PPV23. Study participants were enrolled at five different geographical sites over a 33-month period and followed for up to 6.7 years. Post-recruit training military assignments included diverse geographic locations with potential for crowding and stressors that may have increased *S. pneumoniae* disease risk. After following 152 723 young healthy participants with both active and passive surveillance for radiographically confirmed pneumonias and respiratory disease outcomes, study data suggest no protective benefit from receiving PPV23.

While these data are robust, interpretation should be tempered by knowledge of a number of study limitations. None of our study participants had laboratory evidence of *S. pneumoniae* infection during recruit training. We note that this study began in the year 2000, the same year that vaccination of children <2 years of age with the 7-valent conjugate vaccine was initially recommended in the United States [38]. Since the pediatric conjugate vaccination program has been shown to provide secondary benefits of reducing *S. pneumoniae* disease risk among adults [39], it is possible that the success of the pneumococcal conjugate vaccines also reduced *S. pneumoniae* infection risk among military personnel. However, most military data suggest that such indirect protection has not been realized. In late 2000, Marine Corps Recruit Depot San Diego experienced an outbreak of pneumococcal illness, which prompted universal vaccination of recruits at this site and subsequent disengagement of this site from the vaccine trial [17]. In 2009, 2 fatal cases of *S. pneumoniae* meningitis at another military recruit training camp led to an investigation of *S. pneumoniae* disease and subsequent vaccination of US military personnel at this site. DoD vaccine and medical treatment data show that, despite increasing use of PPV23 among trainees, invasive and noninvasive

pneumococcal disease (inpatient and outpatient) counts have been relatively steady during the period 2000–2008 [40,41].

The study may also have been limited by the procedural change from active surveillance in recruit training to passive surveillance in the subsequent years of diverse military duty assignments. While diagnostic codes are very centric to outpatient and inpatient encounters in DoD medical treatment facilities, capture of acute respiratory disease, pneumonia, meningitis, or other pneumococcal disease depends on the study participant seeking medical care, the provider ordering the appropriate diagnostic tests, the availability and accuracy of tests, and the combined efforts involved in making a specific diagnosis. Hence, it seems logical that we missed some *S. pneumoniae* infections, some pneumonias, and likely considerable acute respiratory disease. However, because the trial was well balanced in randomization, if there was a marked benefit from the vaccine in protecting against any one of the study outcomes, we would have seen some indication of this in the large sample size. We simply saw no evidence of such protection.

Another possible contributor to vaccine non-effect is that administering a protective vaccine to approximately 23% of military trainees might have provided a herd-immunity protective effect. This is particularly possible during recruit training. Training facilities are recognized as high risk environments for acute respiratory disease and pneumonia, comprising a high proportion of total cases in the DoD [14]. A reduction in risk during recruit training could have greatly reduced outcome counts due to pneumococcal disease such that vaccine effectiveness would be difficult to detect. However, as PPV23 has not been shown to affect nasopharyngeal colonization, vaccination would not be expected to reduce the transmission of pneumococcal disease by asymptomatic carriers.

While it would seem that PPV23 should not be indicated for routine use in military trainees, subsets of military personnel may still fall within certain high-risk groups advised for vaccination. The Advisory Committee on Immunization Practices currently recommends PPV23 for all persons aged 65 years or older and for those 18 years of age or older in high-risk groups, including all cigarette smokers, persons with chronic pulmonary disease, and persons with other chronic diseases that affect the immune system. However, with the exception of cigarette smoking, few military personnel would be expected to meet the health indications specified for receipt of adult pneumococcal vaccine. In conclusion, data from this large, double-blind, placebo-controlled trial of PPV23 do not support the routine use of vaccine among healthy new military trainees.

Disclaimer

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to the equivalent product produced by Merck & Co. Inc. (Pneumovax 23).

Author contributions

Dr. Russell served as principal investigator, guided enrollment and data collection, directed data management, provided data interpretation, and led manuscript development. Dr. Baker helped in coordinating the study, training the study team, managed data, helped to interpret the data and to draft the manuscript. Mr. Hansen performed data management and statistical analyses, developed graphics, interpreted the data, and helped to draft the manuscript. Dr. Poland helped to design the study, interpret the data, and to draft the manuscript.

Dr. Ryan helped to execute the study, interpret the data, and to draft the manuscript. Mrs. Merrill interpreted results and collaborated in critically revising the manuscript. Dr. Gray designed the study, won funding and IRB approval for the study, helped to interpret results and to draft the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest statement: G.P. is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. G.P. offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, PAXVAX Inc., and Emergent Biosolutions. G.P. holds two patents related to vaccinia peptide research. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review

Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

The other authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2014.12.058>.

References

- [1] Robbins JB, Austrian R, Lee CJ, Rastogi SC, Schiffman G, Henrichsen J, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983;148:1136–59.
- [2] Update: pneumococcal polysaccharide vaccine usage—United States. *Morb Mortal Wkly Rep* 1984;33:273–327, 81.
- [3] Skull SA, Andrews RM, Byrnes GB, Kelly HA, Nolan TM, Brown GV, et al. Prevention of community-acquired pneumonia among a cohort of hospitalized elderly: benefit due to influenza and pneumococcal vaccination not demonstrated. *Vaccine* 2007;25:4631–40.
- [4] Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. *Clin Infect Dis* 2006;43:860–8.
- [5] Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453–60.
- [6] Fiore AE, Levine OS, Elliott JA, Facklam RR, Butler JC. Effectiveness of pneumococcal polysaccharide vaccine for preschool-age children with chronic disease. *Emerg Infect Dis* 1999;5:828–31.
- [7] Hedlund J, Christenson B, Lundbergh P, Ortvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. *Vaccine* 2003;21:3906–11.
- [8] Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, de Diego C, Valdivieso A, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. *Vaccine* 2009;27:1504–10.
- [9] Vila-Corcoles A, Ochoa-Gondar O, Guzman JA, Rodriguez-Blanco T, Salsench E, Fuentes CM. Effectiveness of the 23-valent polysaccharide pneumococcal vaccine against invasive pneumococcal disease in people 60 years or older. *BMC Infect Dis* 2010;10:73.
- [10] Hirsch EF, McKinney M. An epidemic of pneumococcus bronchopneumonia. *J Infect Dis* 1919;24:594–617.
- [11] McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J Infect Dis* 2003;187:1000–9.
- [12] Hakansson A, Kidd A, Wadell G, Sabharwal H, Svanborg C. Adenovirus infection enhances in vitro adherence of *Streptococcus pneumoniae*. *Infect Immun* 1994;62:2707–14.
- [13] Russell KL, Hawsworth AW, Ryan MA, Strickler J, Irvine M, Hansen CJ, et al. Vaccine-preventable adenoviral respiratory illness in US military recruits, 1999–2004. *Vaccine* 2006;24:2835–42.
- [14] Gray GC, Callahan JD, Hawsworth AW, Fisher CA, Gaydos JC. Respiratory diseases among U.S. military personnel: countering emerging threats. *Emerg Infect Dis* 1999;5:379–85.
- [15] Gray GC, Mitchell BS, Tueller JE, Cross ER, Amundson DE. Pneumonia hospitalizations in the US navy and marine corps: rates and risk factors for 6,522 admissions, 1981–1991. *Am J Epidemiol* 1994;139:793–802.
- [16] Reichler M, Reynolds R, Schwartz B, Musher D, Pratt D, Hohenhaus G, et al. Epidemic of pneumococcal pneumonia in a military training camp [abstract no 49]. In: 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago: American Society for Microbiology; 1991.
- [17] Crum NF, Wallace MR, Lamb CR, Conlin AM, Amundson DE, Olson PE, et al. Halting a pneumococcal pneumonia outbreak among United States Marine Corps trainees. *Am J Prev Med* 2003;25:107–11.
- [18] Sanchez JL, Craig SC, Kolavic S, Hastings D, Alsip BJ, Gray GC, et al. An outbreak of pneumococcal pneumonia among military personnel at high risk: control by low-dose azithromycin postexposure chemoprophylaxis. *Mil Med* 2003;168:1–6.
- [19] Balicer RD, Zarka S, Levine H, Klement E, Sela T, Porat N, et al. Control of *Streptococcus pneumoniae* serotype 5 epidemic of severe pneumonia among young army recruits by mass antibiotic treatment and vaccination. *Vaccine* 2010;28:5591–6.
- [20] Vainio A, Lyytikäinen O, Sihvonen R, Kajjalainen T, Teirila L, Rantala M, et al. An outbreak of pneumonia associated with *S. pneumoniae* at a military training facility in Finland in 2006. *APMIS* 2009;117:488–91.
- [21] Zhogolev SD, Mosiagin VD, Demidovich VU, Mel'nichenko PI, Ogarkov PI. Efficacy of pneumococcal vaccine in military units. *Zh Mikrobiol Epidemiol Immunobiol* 2003;36–42.
- [22] Willems JS, Sanders CR, Riddiough MA, Bell JC. Cost effectiveness of vaccination against pneumococcal pneumonia. *N Engl J Med* 1980;303:553–9.
- [23] Patrick KM, Woolley FR. A cost-benefit analysis of immunization for pneumococcal pneumonia. *JAMA* 1981;245:473–7.
- [24] Beutels P, Postma MJ. Economic evaluations of adult pneumococcal vaccination strategies. *Expert Rev Pharmacoecon Outcomes Res* 2001;1:47–58.
- [25] Vold Pepper P, Owens DK. Cost-effectiveness of the pneumococcal vaccine in the United States Navy and Marine Corps. *Clin Infect Dis* 2000;30:157–64.
- [26] Jones RN, Sader HS, Moet GJ, Farrell DJ. Declining antimicrobial susceptibility of *Streptococcus pneumoniae* in the United States: report from the SENTRY Antimicrobial Surveillance Program (1998–2009). *Diagn Microbiol Infect Dis* 2010;68:334–6.
- [27] Barile A, Driscoll T, Harley D, Haberberger R, Wallace M. Increasing incidence of penicillin-resistant *Streptococcus pneumoniae*. In: Proceedings of the IDSA 35th Annual Meeting. 1997.
- [28] Zhogolev SD, Ogarkov PI, Mel'nichenko PI. The prophylaxis of nonhospital pneumonia using 23-valent pneumococcus vaccine in the military collectives. *Voen Med Zh* 2004;325:35–43, 96.
- [29] Murray PR. American society for microbiology. Manual of clinical microbiology. 6th ed. Washington, DC: ASM Press; 1995.
- [30] Isenberg HD. American society for microbiology. Clinical microbiology procedures handbook. Washington, DC: American Society of Microbiology; 1992.
- [31] Kalin M, Kanclerski K, Granstrom M, Mollby R. Diagnosis of pneumococcal pneumonia by enzyme-linked immunosorbent assay of antibodies to pneumococcal hemolysin (pneumolysin). *J Clin Microbiol* 1987;25:226–9.
- [32] Campbell LA, Perez Melgosa M, Hamilton DJ, Kuo CC, Grayston JT. Detection of *Chlamydia pneumoniae* by polymerase chain reaction. *J Clin Microbiol* 1992;30:434–9.
- [33] Persing DH. Diagnostic molecular microbiology: principles and applications. Washington, DC: American Society for Microbiology; 1993.
- [34] Abele-Horn M, Busch U, Nitschko H, Jacobs E, Bax R, Pfaff F, et al. Molecular approaches to diagnosis of pulmonary diseases due to *Mycoplasma pneumoniae*. *J Clin Microbiol* 1998;36:548–51.
- [35] de Barbeyrac B, Bernet-Poggi C, Febrer F, Renaudin H, Dupon M, Bebear C. Detection of *Mycoplasma pneumoniae* and *Mycoplasma genitalium* in clinical samples by polymerase chain reaction. *Clin Infect Dis* 1993;17(Suppl 1):S83–9.
- [36] Ieven M, Ursi D, Van Bever H, Quint W, Nieters HG, Goossens H. Detection of *Mycoplasma pneumoniae* by two polymerase chain reactions and role of *M. pneumoniae* in acute respiratory tract infections in pediatric patients. *J Infect Dis* 1996;173:1445–52.
- [37] Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2000;49:1–35.
- [38] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;348:1737–46.
- [39] Field investigation: fatal *Pneumococcal meningitis*, Fort Leonard Wood, Missouri, February 2009. *MSMR* 2009;16:2–6.
- [40] Surveillance snapshot: immunization against and incidence of pneumococcal disease. *MSMR* 2009;16:7.

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14. ABSTRACT <p>Background: Streptococcus pneumoniae infections have periodically caused significant morbidity and outbreaks among military personnel, especially trainees. This study evaluated the effectiveness of the 23-valent polysaccharide pneumococcal vaccine (PPV23) in reducing pneumonia in healthy military trainees.</p> <p>Methods: From 2000–2003, 152 723 military trainees from 5 US training camps were enrolled in a double-blind, placebo-controlled trial of PPV23. Participants were closely monitored during basic training for radiographically confirmed pneumonia etiology and loss-of-training days. Participants were also followed using electronic medical encounter data until 1 June 2007 for three additional outcomes: any-cause pneumonia, any acute respiratory disease, and meningitis.</p> <p>Results: Comparison of demographic data by study arm suggested the randomization procedures were sound. During basic training, 371 study participants developed radiographically confirmed pneumonia. None had evidence of S. pneumoniae infection, but other etiologies included adenovirus (38%), Chlamydia pneumoniae (9%), and Mycoplasma pneumoniae (8%). During the follow-up period, many study participants, in both the vaccine and placebo groups, had clinical encounters for the medical outcomes of interest. However, Cox's proportional hazard modeling revealed no evidence of a protective vaccine effect during recruit training (radiographically confirmed pneumonia) or up to 6.7 years after enrollment (any-cause pneumonia, any acute respiratory disease, or meningitis).</p> <p>Conclusions: Data from this large, double-blind, placebo controlled trial do not support routine use of PPV23 among healthy new military trainees. This clinical trial was registered at clinical-trials.gov (registration number NCT02079701, http://www.clinicaltrials.gov/ct2/show/NCT02079701?term=NCT02079701&rank=1).</p>					
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